Ornithine and Homocitrulline Induce Oxidative Damage in Cerebellum of Young Rats

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INTRODUCTION: Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome is an inherited metabolic disorder biochemically characterized by tissue accumulation of ornithine (Orn), ammonia and homocitrulline (Hcit) and clinically by cerebellar ataxia, choreoathetosis and other symptomatology. Considering that the pathophysiology of the cerebellar symptoms of this disorder is virtually unknown, the aim of the present work was to investigate the in vitro effects of Hcit and Orn (0.1 - 5mM) on important parameters of oxidative stress and energy metabolism in cerebellum of 30-day-old rats.

MATERIAL AND METHODS: We measured thiobarbituric acid-reactive substances (TBA-RS) levels, reduced glutathione (GSH) concentrations, sulfhydryl content, carbonyl formation, aconitase and α-ketoglutarate dehydrogenase activities.

RESULTS AND DISCUSSION: Orn and Hcit significantly increased thiobarbituric acid-reactive substances (TBA-RS) levels, implying that lipid peroxidation was induced in rat cerebellum. Furthermore, Orn-induced elevation of TBA-RS was prevented by melatonin and GSH, indicating that these effects were due to reactive oxygen species that are scavenged by these antioxidants. Furthermore, the nitric oxide inhibitor L-NAME did not alter the induction of lipid oxidation and nitric oxide production was not affected by Orn and Hcit. It is therefore presumed that reactive nitrogen species were not involved in these effects. In addition, Orn and Hcit significantly decreased non-enzymatic antioxidant defenses determined by glutathione (GSH) levels. Orn also induced sulfhydryl oxidation. In contrast, carbonyl formation was not altered by Orn or Hcit. Finally, we observed that Orn and Hcit reduced aconitase activity, but did not alter α-ketoglutarate dehydrogenase activity.

CONCLUSION: Therefore, it is conceivable that disruption of redox homeostasis by Orn and Hcit may be involved in the pathophysiology of the cerebellar ataxia characteristic of the patients affected by HHH syndrome.

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